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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,854	03/07/2002	Felix Kratz	25048/20	6344

7590 07/20/2006

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,854	KRATZ, FELIX	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20011211*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. As set forth in the Examiner Interview Summary Record dated February 11, 2004, the restriction requirement mailed January 28, 2004 is withdrawn.

Applicant's election of the species in the reply filed on November 13, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 21 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 13, 2003.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The Sequence Listing filed February 6, 2006 was not accompanied by a statement that the computer readable form copy and the paper copy of the Sequence Listing are the same, as is required by 37 CFR 1.825(b). Correction is required.

The Sequence Listing filed February 6, 2006 was approved by STIC for matters of form.

3. The disclosure is objected to because of the following informalities: SEQ ID NOS need to be inserted after all amino acid sequences subject to the sequence disclosure rules. See 37 CFR 1.821(d). Such sequences are present at pages 23, 24, and 35-37 of the specification, and in Figure 2B. For sequences present in the drawings, the SEQ ID NOS are preferably inserted into the Brief Description of the Drawings. Applicants are requested to re-supply by appropriate

amendment the top line of page 25 of the specification. The current scanned image is partially obscured due to hole punching in the original source. Appropriate correction is required.

4. Claims 18-20, 22-24, 26, 27, and 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 is indefinite because it is not clear what is intended by using "consisting essentially of" to define the drug moiety. It is not clear what is intended to be excluded as a possible drug moiety through the use of "consisting essentially of" rather than "comprising" terminology; alternatively, it is not clear what variations might be permitted in the specified compounds through the use of "consisting essentially of". There is no antecedent basis in the claim for the phrase "the linkage" at claim 18, lines 10-12. The claim does not previously indicate that the drug moiety, spacer molecule, and/or thiol binding group are linked. At claim 26, line 5, it is not clear if "which" refers to the immediately preceding acetylene group, or if it refers to all of the specific thiol-binding groups recited in the claim.

5. Claims 18-20, 22-24, 26, 27, and 31-34 are objected to because of the following informalities: At claim 18, lines 3 and 16, "cysteine" is misspelled. At claim 24, lines 3 (second occurrence) and 4, "the" should be deleted in order to avoid issues of antecedent basis. At claim 24, line 8, "or" should be changed to "and" so that standard Markush terminology is used. At claim 26, line 2, "one of" should be deleted. At claim 34, line 2, "a" should be changed to "the" so that standard Markush terminology is used. At claim 34, line 4, "and" should be inserted after the comma so that standard Markush terminology is used. Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no original disclosure supporting the claim limitation that the pharmaceutical can be an antipyretic, as is recited in instant claim 25. Antipyretics are not mentioned as possible drugs in the specification or original claims.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art

may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

8. Claims 18, 20, 22-24, and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by the Firestone et al article (Journal of Controlled Release, Vol. 39, pages 251-259). The Firestone et al article teaches carrier-drug conjugates comprising doxorubicin conjugated to a monoclonal antibody carrier. The monoclonal antibody, BR96, has eight reducible cysteine groups. The BR96 is treated with dithiothreitol and is then reacted with doxorubicin-6-maleimidocaproylhydrazone to produce conjugates having a molar ratio of doxorubicin:BR96 of 5.70:1 and 6.94:1 (which equal ratios of doxorubicin:reducible cysteine groups of 0.71:1 and 0.87:1). The spacer comprises a peptide bond between the hydrazone group and the caproyl group. The conjugates are internalized into cells, where the spacer is cleaved in the acid environment. The conjugates exhibit antitumor activity. See, e.g., page 252, column 1, first full paragraph, and column 2, lines 7-11; page 253, column 1, first full paragraph, and Scheme 2; Table 2. With respect to instant claims 33 and 34, the conjugate of the Firestone et al article is deemed to anticipate the instant kit claims, whose only recited element is the carrier-drug conjugate.

9. Claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being obvious over the Firestone et al article (Journal of Controlled Release, Vol. 39, pages 251-259). Application of the Firestone et al article is the same as in the above rejection of claims 18, 20, 22-24, and 26-34. To the extent that the Firestone et al article might not teach its conjugate in kit form, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to

package the conjugate of the Firestone et al article in kit form because kits are routinely used in the pharmaceutical arts for purposes of storage, transportation, measurement, and administration.

10. Claims 18-20, 22-24, 26, 27, and 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/10794. (The examiner will rely upon U.S. Patent No. 6,310,039 as a translation of the WO Patent Application '794. All citations in this rejection are to the U.S. patent.) The WO Patent Application '794 teaches a carrier drug conjugate in which doxorubicin is linked via a hydrazone linkage through phenylacetic acid to a maleimide group, which is conjugated to thiolated albumin. Seven molecules of doxorubicin are linked per molecule of albumin. See, e.g., column 22, lines 33-42. Hydrazone linkages are hydrolyzable in acidic mediums. Because there is one reducible cysteine group per molecule of albumin, the ratio of doxorubicin bound per mole of reducible cysteine group in the conjugates of the WO Patent Application '794 is 7. Note that while claim 18 requires the carrier to comprise at least one reducible cysteine group, it does not actually require the cysteine group to be in reduced form; and that while the claim recites a ratio of bound drug per reducible cysteine group, it does not actually require that the drug be bound to the cysteine group. With respect to instant claims 33 and 34, the conjugate of the WO Patent Application '794 is deemed to anticipate the instant kit claims, whose only recited element is the carrier-drug conjugate.

11. Claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 98/10794. Application of the WO Patent Application '794 is the same as in the above rejection of claims 18-20, 22-24, 26, 27, and 31-34. To the extent that the WO Patent Application '794 might not teach its conjugate in kit form, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the conjugate of

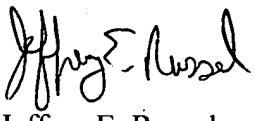
the WO Patent Application '794 in kit form because kits are routinely used in the pharmaceutical arts for purposes of storage, transportation, measurement, and administration.

12. Claims 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Schlag et al (U.S. Patent No. 6,124,255). Schlag et al teach subjecting albumin to treatment with a 10- to 20-fold oar excess of mercaptoethanol in order to form free SH groups, and then nitrosating the thiol groups. See, e.g., Example 2. The nitroso groups of Schlag et al correspond to Applicants' drug. In view of the similarity in reactants and method steps, inherently Schlag et al will achieve the same proportion of cysteine SH groups and the same degree of purity as are claimed by Applicant. Sufficient evidence of similarity is deemed to be present between the method of Schlag et al and Applicant's claimed method to shift the burden to Applicant to provide evidence that the claimed method is unobviously different than that of Schlag. Note that Applicant's method claims, in contrast to Applicant's conjugate claims, do not require the presence of a spacer molecule.

13. The Narazaki et al article, cited on the Information Disclosure Statement filed December 11, 2001, has been crossed off because a copy of the reference does not appear to have been provided, and a copy is not readily available to the examiner. Applicant is requested to supply a copy of the reference with the response to this Office action so that the examiner can consider the reference and make it of record.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

July 14, 2006